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(54) Title: ASYMMETRIC SYNTHESIS OF (R)- AND (S)-ARYLETHANOLAMINES FROM IMINOKETONES

(57) Abstract

A method for the enantioselective reduction of an α -iminoketone to an α -aminoalcohol is disclosed. The method utilizes a borane reducing agent as the reducing agent and a chiral 1,3,2-oxazaborole as the catalyst. The method is applied to the synthesis of R-albuterol from methyl 5-acetylsalicylate in high yield and high optical purity.

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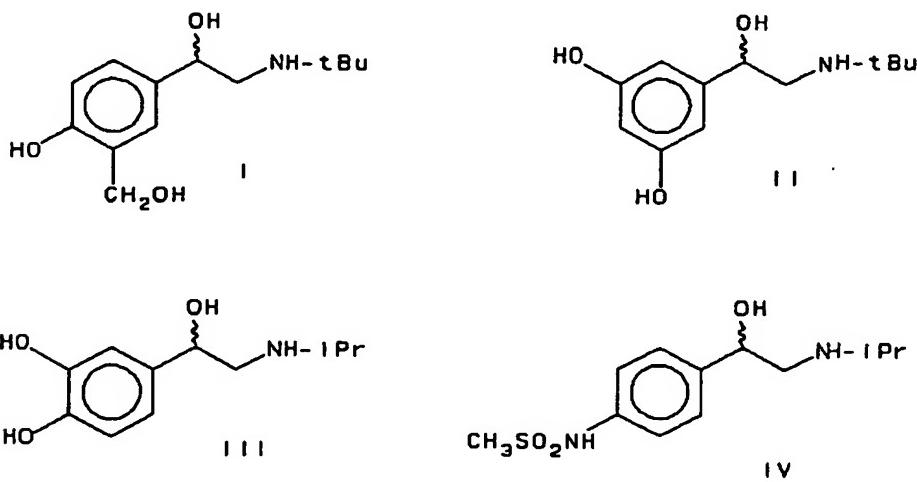
**ASYMMETRIC SYNTHESIS OF (R)- AND (S)-
ARYLETHANOLAMINES FROM IMINOKETONES**

Field of the Invention

5 The invention relates to a method for the enantiospecific reduction of an α -iminoketone to an α -aminoalcohol, particularly an arylethanamine. The method comprises reacting an α -iminoketone with a borane reducing agent in the presence of a 1,3,2-
 10 oxazaborolidine catalyst.

Background of the Invention

2-Amino-1-arylethanol derivatives, such as albuterol (I), terbutaline (II), isoproterenol (III), and sotalol (IV), are well known pharmaceutical
 15 agents.



These and other β -adrenergic agents (β -blockers or β -agonists) are used in the treatment of asthma, glaucoma and cardiovascular diseases. As a class, the 2-amino-1-arylethanol possess at least one

enantiogenic center. It is often the case that two enantiomers of a chiral drug display different biological activities, and although the enantiomers of many arylethanolamine drugs appear to exhibit this 5 dichotomous activity, to date only a few optically pure arylethanolamine drugs have been prepared. This is probably because the synthetic approaches to arylethanolamines generally involve (1) tedious diastereomeric resolutions, (2) high-cost reagents, 10 or (3) lengthy multistep syntheses with low overall yields. In fact, the only published method for preparation of an optically pure albuterol enantiomer is by the resolution of a benzyl-protected ester precursor [Hartley and Middlemiss, J. Med. Chem. 14, 895 (1971)]. A simple synthesis of 15 enantiomerically pure arylethanolamines would be highly desirable.

Initially one might consider the enantiospecific reduction of the ketone functionality in an α -aminoketone, because α -aminoketones are common 20 intermediates in the syntheses of the above-mentioned β -agonists and β -blockers.

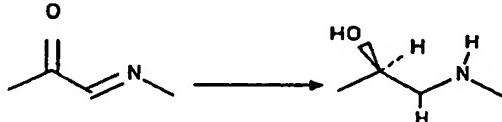


It has been reported that asymmetric hydrogenation of α -amino ketones in the presence of a ruthenium 25 complex gives α -aminoalcohols with high enantioselectivity. However, catalytic hydrogenation is often less attractive than hydride-type reductions in that, with hydrides or borane, additional functionalities (such as the ester in an albuterol

precursor) can, in principle, be reduced in the same step as the ketone.

Asymmetric reductions of prochiral ketones with borane in the presence of chiral oxazaborolidine catalysts are known, and high enantioselectivities have been observed with many ketones. Unfortunately, the high enantioselectivity observed with simple ketones has not been achieved in asymmetric borane reduction of α -amino substituted ketones, which give products characterized by disappointingly low enantiomeric excesses (ee).

α -Iminoketones are one step closer to starting material, and the simultaneous reduction of both the ketone and the imine functionalities would eliminate one step in the overall synthesis.



The known racemic mixture of albuterol isomers(I) has, in at least one instance, been prepared by the chirally uncontrolled reduction of an α -imino ketone intermediate (PCT WO 92/04314). There are a few reports on the asymmetric reduction of the C=N functionality with borane, and in the few that have been reported, moderate asymmetric induction has been obtained in some cases [See Cho et al. J.Chem. Soc. Perkin Trans. I, 1990, 3200; and Cho et al. Tetrahedron: Asymmetry, 3, 337 (1992).] However, no methods appear to have been reported for the asymmetric reduction of α -imino ketones to give α -

aminoalcohols.

Summary Of The Invention

It is an object of the present invention to provide a general method for the synthesis of 5 optically pure (R)- and (S)-albuterol and similar ethanolamines via the asymmetric reduction of α -iminoketone precursors.

It is a further object to provide a method that 10 is inexpensive and provides reproducible, high yields.

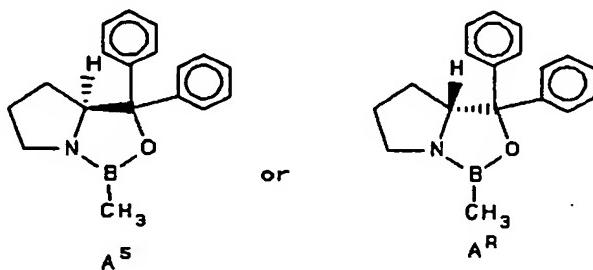
It is an advantage of the process of the invention that it allows the reduction of additional functionalities, such as esters, in the same step as the asymmetric reduction of the iminoketone.

15 It is a further advantage of one particular embodiment of the invention that it proceeds from an intermediate in an industrial process for albuterol.

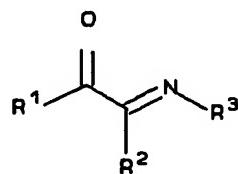
These and other objects features and advantages 20 are provided by the present invention, which in one aspect relates to a process for the enantiospecific reduction of an α -iminoketone to an α -aminoalcohol comprising reacting an α -iminoketone with a borane reducing agent, such as borane-dimethyl sulfide or borane-THF, in the presence of a chiral 1,3,2- 25 oxazaborole catalyst. For convenience, the catalysts of the invention will often be referred to in the text as "oxazaborolidines"; in fact, following strict Chemical Abstracts nomenclature, they would be named as derivatives of pyrrolo-oxazaborole, the "idine"

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suffix conveying the same oxidation state as the "tetrahydro" substituent nomenclature. A preferred catalyst is tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole (A) or its borane complex:



Suitable α -iminoketones include, among others, compounds of formula V



V

wherein

- 10 R¹ is phenyl, substituted phenyl, naphthyl, substituted naphthyl, heteroaryl or substituted heteroaryl;
- R² is hydrogen, aryl or lower alkyl; and
- 15 R³ is secondary or tertiary alkyl or an aryl group.

In a preferred embodiment R² is hydrogen; in further preferred embodiments R¹ is phenyl or substituted phenyl, R² is hydrogen and R³ is isopropyl or tert-butyl. In a particularly preferred embodiment a precursor to albuterol is reduced to albuterol. The

precursor to albuterol can be reduced to predominantly (R)-albuterol in the presence of (R)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole.

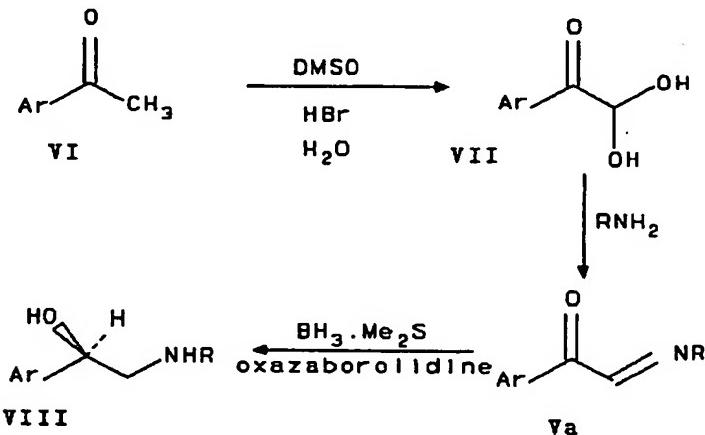
5 In one specific aspect the invention relates to a process for producing (S)-albuterol by reacting methyl 5-((1,1-dimethylethyl)imino)acetyl-2-hydroxybenzoate with borane-dimethylsulfide in the presence of (S)-tetrahydro-1-methyl-3,3-diphenyl-10 1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole or its borane complex.

In another specific aspect, the invention relates to a process for producing (R)-albuterol comprising reacting methyl 5-((1,1-dimethylethyl)imino)acetyl-2-hydroxybenzoate with borane-dimethylsulfide in a suitable solvent in the presence of (R)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]-oxazaborole. A preferred solvent is toluene. The reaction is optimally carried out at a temperature between about -20°C and +20°C, and is carried out either (a) by adding a solution of methyl 5-((1,1-dimethylethyl)imino)acetyl-2-hydroxybenzoate to a solution of borane-dimethylsulfide and (R)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole; or (b) by adding a solution of methyl 5-((1,1-dimethylethyl)imino)acetyl-2-hydroxybenzoate and a solution of borane-dimethylsulfide simultaneously to a solution of (R)-tetrahydro-1-methyl-3,3-diphenyl-30 1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole.

**Detailed Description Inclusive of
Preferred Embodiments**

The general synthesis of arylethanolamines of the invention is shown in Scheme A. The method is particularly simple and practical because it proceeds via readily available α -iminoketones (Va):

Scheme A



The graphic representations of racemic, ambiscalemic and scalemic or enantiomerically pure compounds used herein are taken from Maehr J. Chem. Ed. 62, 114-120 (1985). Thus, solid and broken wedges (as in A) are used to denote the absolute configuration of a chiral element; wedge outlines and dotted or broken lines (e.g. VIII) denote enantiomerically pure compounds of indeterminate absolute configuration. As usual, a wavy line indicates a mixture of enantiomers of indeterminate proportion, commonly a racemic mixture.

The term "enantiomeric excess" is well known in the art and is defined for a resolution of $ab \rightarrow a + b$ as

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$$ee_a = \left(\frac{\text{conc. of } a - \text{conc. of } b}{\text{conc. of } a + \text{conc. of } b} \right) \times 100$$

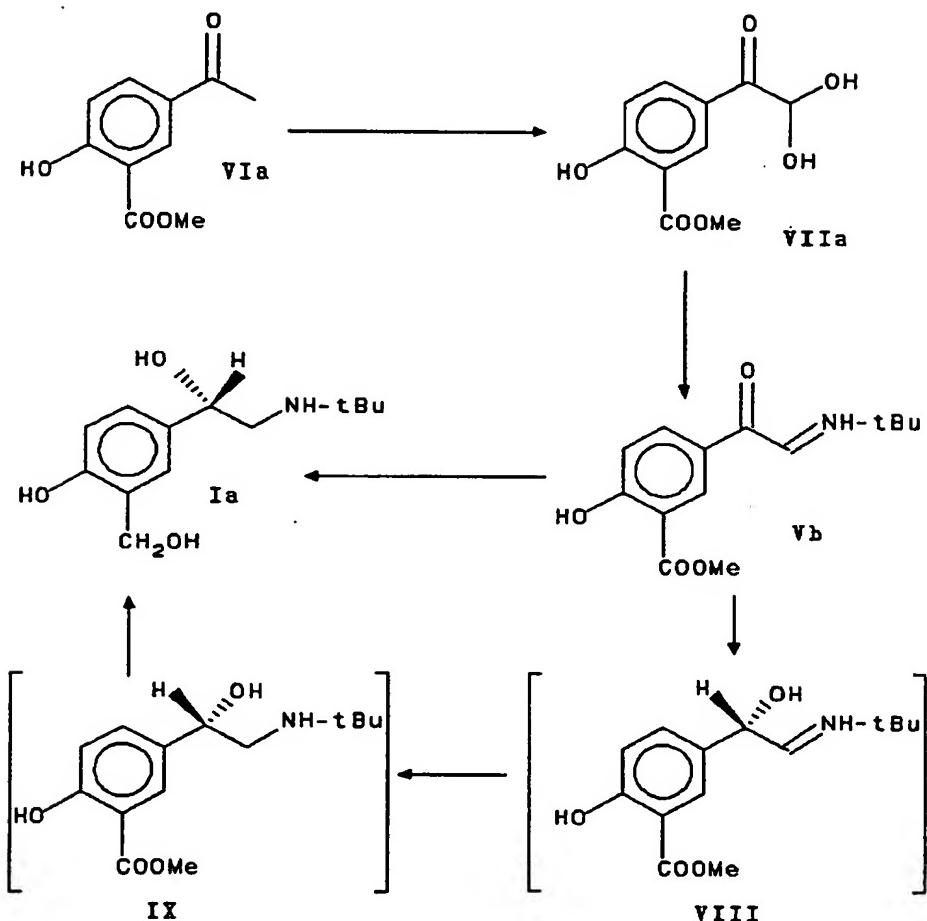
- The term "enantiomeric excess" is related to the older term "optical purity" in that both are measures of the same phenomenon. The value of ee will be a number from 0 to 100, zero being racemic and 100 being pure, single enantiomer. A compound which in the past might have been called 98% optically pure is now more precisely described as 96% ee. Processes that yield products of ee less than about 80% are not generally regarded as commercially attractive.
- 5 Processes that yield albuterol of ee greater than about 96% are particularly attractive because the eutectic of albuterol is about 96-97%, and thus substantially pure single enantiomers can be obtained by simple recrystallization of the product.
- 10 Arylglyoxals (VII) are most conveniently prepared from acetophenone derivatives by the procedure of PCT application 92/04314, although other syntheses, well known to persons of skill in the art, are also suitable.
- 15 In the case of albuterol, the starting material, methyl 5-acetylsalicylate (VIa), is commercially available. Oxidation in DMSO (1.0 M) in the presence of 2 equivalents of aqueous HBr proceeds smoothly at 60 °C over 20 hours in greater than 80% yield to give 20 the arylglyoxal (VIIa) as a yellow solid. Without further purification, this compound is treated with 1.0- 1.2 eq of t-BuNH₂ in warm toluene or ethyl acetate to give the iminoketone (Vb) in greater than 25 70% yield. The iminoketone can be purified by 30 recrystallization from toluene/heptane and is used in

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the reduction after drying. Overall yield from the salicylate is greater than 60%.

The complete synthesis is outlined in Scheme B.

Scheme B



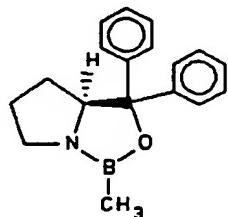
5 The reduction with three equivalents of borane is depicted as proceeding through the intermediate imine-alcohol-ester VIII and aminoalcohol-ester IX to the aminodiol Ia, but the intermediates have not been

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isolated or identified; the sequence is presented for heuristic purposes only.

The advantages of this route are: (a) it follows an industrial process for racemic albuterol that has
5 been developed for the production of racemic albuterol in multi kilo quantities; (b) it is short (only three steps); and (c) it represents a new general method applicable to the synthesis of related optically active arylethanamine derivatives such as
10 salmeterol, etilefrine, isoproterenol, terbutaline, etc.

The optimal catalyst for a particular substrate is a matter of experimentation. For albuterol five catalysts were examined: catalyst A, the catalyst of
15 choice, was tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]-oxazaborole (A) or its borane complex;



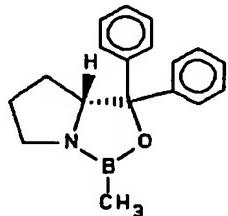
A

catalyst B was 4,5-diphenyl[1,3,2]oxazaborolidine;
20 catalyst C was 4,5-diphenyl-2-methyl-[1,3,2]-oxazaborolidine; catalyst D was 3,3a,8,8a-tetrahydro-2H-indeno[1,2-d][1,3,2]oxazaborole; and catalyst E was 5,5-diphenyl-4-[2-(methylthio)ethyl][1,3,2]-oxazaborolidine. Catalyst A was prepared according
25 to the method of Mathre et al. [J. Org. Chem. 58,

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2880-2888 (1993)]; catalysts B and C were prepared by the method of Quallich and Woodall [Syn. Lett. 1993, 929]; catalyst D was prepared *in situ* from (1S,2R)-*cis*-1-amino-2-indanol; and catalyst E was 5 prepared *in situ* according to the procedure of Mehler and Martens [Tetrahedron: Asymmetry 4, 1983 and 2299 (1993)].

The above catalysts were tested in the reduction of the iminoketone precursor Vb under similar 10 conditions (some variations based on further experiments, *vide infra*). The best result was obtained with catalyst A. The absolute configuration of albuterol product was determined by HPLC using a reference standard. It was found that in the case of 15 albuterol, the S-enantiomer predominated when using S-catalysts derived from natural L-amino acids (e.g. L-proline). Thus, in order to prepare (R)-albuterol, the preferred R-catalyst (A^R)



A^R

20 has to be prepared from D-proline. The results are summarized in Table 1. Based on these results, catalyst A was used in subsequent studies.

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Table 1

**Nature of the catalysts in reduction
of ketoimine (3)***

Entry	Condition	Catalyst (mol%)	ee(%) ^b	Conversion (%)
5	1 toluene, rt, slow addition	A (20%)	76(S)	>99
	2 CH ₂ Cl ₂ , -20°C, slow addition	B (20%)	6(S) ^c	99
	3 toluene, rt, slow addition	C (100%)	33(S)	89
	4 toluene, rt, slow addition	D (100%)	70(S)	99
	5 CH ₂ Cl ₂ , rt, slow addition	E (20%)	25(S)	100

10 * Reactions were performed under the standard conditions (see Experimental section) except as noted.

15 ^b ee were determined by HPLC on a Sumichiral OA 4900 column or equivalent.

^c Low ee may have been due to impure catalyst.

It is often observed in asymmetric catalysis that the order and conditions of addition of reagents and substrate significantly affect the degree of asymmetric induction. Although no detailed study of this effect appears in the literature for the asymmetric reduction of ketones with borane in the presence of the oxazaborolidine catalyst, the reduction is usually performed by adding the substrate last in the chosen solvent. Initially, the reduction of iminoketone with borane was performed in this manner by mixing all components together. However, as shown in Table 2, the ee of albuterol

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obtained was disappointingly low (entry 1).

By slow addition of the iminoketone over a period of 3 hours to the solution of borane and the catalyst, the enantioselectivity increased dramatically (entries 2 and 4). The enhanced enantioselectivity may be due to the fact that under these conditions, the effective concentration of the catalyst is higher. It may also be that the keto group is reduced faster than the imine group, and the resulting intermediate imine-alcohol (VIII) does not complex with borane as strongly as the catalyst does to affect the asymmetric induction. When the iminoketone and borane were added simultaneously to the catalyst solution over a period of 3 hours, slightly higher ee's were obtained (entries 3 and 5).

Table 2
Effects of addition manner

Entry	Addition manner and condition (20 mol % A)	ee (%)	Conversion (%)
1	CH ₂ Cl ₂ , -20° C, all together	5-35	85-100
2	CH ₂ Cl ₂ , -20° C, sm added slowly (3 h)	83	>99
3	toluene, -20° C, sm and BH ₃ added slowly (3 h)	83	>99
4	toluene, 20° C, sm added slowly (3 h)	76	>99
5	toluene, 20° C, sm and BH ₃ added slowly (3 h)	85	>99

Two solvents, toluene and methylene dichloride, were examined. The literature indicates that higher ee are obtained in the reduction of simple ketones in CH₂Cl₂, than in toluene. In the present invention,

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toluene gives higher ee in the reduction of the iminoketone with 20 mol% catalyst A, as shown in Table 3. This is an unexpected advantage, since toluene is much preferred over CH₂Cl₂, for industrial processes.

Table 3
Effects of solvent

Entry	Solvent	Conditions	ee(%)	Conversion (%)
10	CH ₂ Cl ₂	-20° C, sm added slowly	83	>99
	Toluene	-20° C, sm added slowly	87	99

Both stereoselectivity and chemoselectivity commonly depend on the reaction temperature. This effect was examined in more detail using 20 mol% catalyst A by slow addition of the iminoketone over 3 to 4 hours. The results are presented in Table 4. At -40° C or below, the reaction was slow, and after warming up to normal temperature, low ee product was obtained due to presence of excess of starting material. At -20° C good selectivity was observed. Little difference in selectivity was observed between reactions at 0° C and at -20° C; 0° appears to be a convenient temperature.

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Table 4
Effects of temperature

Entry	Solvent	Temperature (°C)	ee(%)	Conversion (%)
5	CH ₂ Cl ₂	-40	36	88
	CH ₂ Cl ₂	-20	83	>99
	CH ₂ Cl ₂	0	83	94
	toluene	-20	87	99
	toluene	-20	86	>99
	toluene	20 (10 mol% A)	76	99
10	toluene	20 (simultan. add.)	85	100

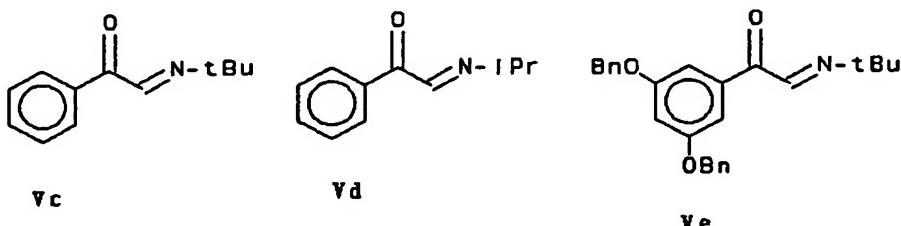
It is desirable to minimize the amount of catalyst used in the reduction. To obtain the ceiling ee in this reduction, a reaction with 100 mol% catalyst A was performed and albuterol of 97% ee was obtained. As shown in Table 5, when the reaction was performed by simultaneous addition of the iminoketone and borane to the catalyst solution in toluene at 0° C, ee's in the range of 93-95% could still be obtained with only 10 mol% catalyst. This is an industrially practical range for the preparation of optically pure albuterol.

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Table 5
Effects of catalyst loading

Entry	Conditions	mol% of A	ee(%)	Conversion (%)
5	CH ₂ Cl ₂ , sm added slowly (3 h), -20° C	20	83	>99
	CH ₂ Cl ₂ , sm added slowly (3 h), -20° C	100	97	85
	same as above, 5 h addition	10	44.2	>99
	CH ₂ Cl ₂ , simultan. add over 5 h	10	72.7	96
	toluene, 0° C, sm added slowly (3 h)	50	95.5	100
	toluene, 0° C, simultan. addition	30	96	>99
	toluene, same as above	10	93	>99
	toluene, same as above	10	95	>99

The extension of the method to other chiral arylethanolamines such as salmeterol, etilefrine, isoproterenol, terbutaline, Beecham's BRL 35,135 and 15 BRL37,344 and Lederle's CL 316,243, is illustrated by the asymmetric reductions of the model iminoketones Vc, Vd and Ve:



The ketoimines were prepared by reaction of the corresponding arylglyoxal with branched primary

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amines such as t-butylamine and isopropylamine. An attempt to isolate the ketoimine from the reaction of an arylglyoxal with a straight chain primary amine failed, perhaps because of the instability of the product ketoimine (polymerization and hydrolysis).
 5 However, it is believed that the process will be effective with any imine (straight chain or otherwise) that can be obtained in pure form.
 Iminoketone Vc is a model compound for albuterol.
 10 Iminoketone Vd is a model compound for BRL35,135, BRL 37,344, CL 316,243, isoproterenol, metaproterenol, sotalol and labetalol. Iminoketone Ve is a precursor for terbutaline. (It leads to terbutaline after debenzylation with H₂, Pd/C). The results of
 15 asymmetric reductions of iminoketones Vc-Ve are summarized in Table 6.

Table 6
Variation of substrates*

Entry	Substrate	mol% A	ee(%)	Yield (%)**
20	Vc	20	85	99
	Vd	20	93	71
	Ve	20	(85-90)***	90

* Reactions were performed in toluene at 0 C by simultaneous addition of ketoimine and borane to the catalyst solution.
 25

** Yields are isolated yields.

*** Estimated value, HPLC method is not available.

30 Thus, a new practical and general method for the preparation of optically active (S)- and (R)-albuterol and other arylethanolamines has been developed. This method represents the preferred

process for the synthesis of these compounds because the process consists of only three steps and the asymmetric induction is catalytic in nature.

Catalyst A or its borane complex appears to be best
5 for albuterol. Albuterol of 93-95% ee can be obtained with 10 mol% catalyst under the optimized conditions. Good results are obtained using toluene as solvent, thus making the process more industrially practical.

10 Examples

The synthesis of arylglyoxal (VIIa) follows a modified literature procedure (Floyd, M.B., et al. J. Org. Chem. 50, 5022 (1985)) and is described here for methyl 5-acetylsalicylate (VIa).

15 A 500 mL three neck flask was charged with 150 mL of DMSO and methyl 5-acetylsalicylate (39 g, 0.2 mol). Aqueous HBr (48%, 46 mL, 0.4 mol, 2.0 eq) was added dropwise over 30 min. After addition, the solution was heated at about 60° C for about 20 hours
20 (followed by TLC or HPLC) until the disappearance of starting material. The yellow mixture was poured onto 400 g of ice with stirring. After stirring for 30 min, the yellow solid was collected by filtration and washed with 2 x 50 mL of cold water and toluene
25 to give the arylglyoxal (VIIa) (crude yield ca. 80% based on dried material). The wet solid was dried at room temperature under vacuum for 4 hours and used in the next step without further purification.

Reaction of arylglyoxal (VIIa) with t-butylamine
30 to give iminoketone (Vb) was performed in toluene or ethyl acetate as follows:

The wet solid from above (1.0 eq, based on

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0.2 mol, 100% yield) and 1.1 eq of t-butylamine (0.22 mol, 23 mL) were dissolved in 200 mL of toluene. The solution was heated at about 40° C for about 2 hours. The solution was then cooled to room temperature and 5 washed with brine (2 x 50 mL) and concentrated to dryness under vacuum to give crude iminoketone (Vb) as a yellow solid (33.4 g, 63% yield from methyl 5-acetylsalicylate). The crude iminoketone can be further purified by recrystallization from 10 toluene/heptane to give pure iminoketone (Vb).

The reduction of iminoketone (Vb) with 10 mol% of catalyst A was as follows:

A 25 mL three neck flask equipped with a refluxing condenser and a thermometer was charged 15 with 2 mL of anhydrous toluene and 0.1 mmol of catalyst A^s (10 mol%) at room temperature under nitrogen. After cooling to 0° C, 300 µl of BH₃Me₂S (BMS) (10 M, 2.0 mmol, 3.0 eq) and a solution of 1 mmol of ketoimine (Vb) (1.0 eq) in 3 mL of toluene 20 were added simultaneously via syringe over 3 hours at 0° C. After addition, the solution was stirred for an additional hour, then was heated to reflux for 5 hours. After cooling to 5° C, the reaction mixture was quenched with 2 mL of methanol. The resulting 25 solution was stirred at room temperature for 10 minutes and then at reflux for 3 hours. The solvent and methanol were removed by distillation. The residual white solid was washed with 3 x 6 mL of 2:1 hexane/ethyl acetate at 50-60° C. The solid was 30 further purified by passing through a short pad of silica gel (0.5 cm) eluting with methanol. After removal of methanol, optically active (S)-albuterol was obtained in >90% yield; the ee was found by HPLC to be 93-95% (Sumichiral OA 4900 column. Mobile

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phase: hexane/CH₂Cl₂/MeOH/CF₃CO₂H(240:140:20:1); Flow
rate: 1mL/min; Detector: UV 280 nm; Injection
volume: 20 μ l of 1 mg/mL sample).

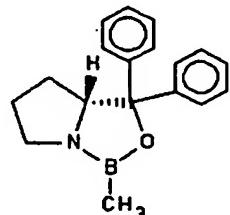
While the invention has been particularly shown
5 and described with reference to preferred embodiments
thereof, it will be understood by those skilled in
the art that other changes in form and details may be
made therein without departing from the spirit and
scope of the invention.

-20-

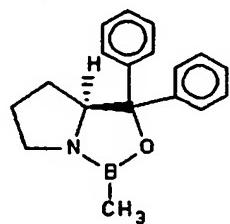
CLAIMS

1. A process for the enantiospecific reduction of an α -imino ketone to an α -amino alcohol comprising reacting an α -imino ketone with a borane-reducing agent in the presence of a chiral 1,3,2-oxazaborole catalyst.

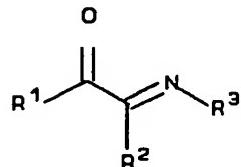
2. A process according to claim 1 wherein said 1,3,2-oxazaborole catalyst is (R) tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-c][1,3,2]oxazaborole or its borane complex:



3. A process according to claim 1 wherein said 1,3,2-oxazaborole catalyst is (S) tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-c][1,3,2]oxazaborole or its borane complex:



4. A process according to claim 1 wherein said α -iminoketone is of the formula



wherein

- R^1 is phenyl, substituted phenyl, naphthyl
5 substituted naphthyl, heteroaryl or substituted heteroaryl;
- R^2 is hydrogen, aryl or alkyl; and
- R^3 is secondary or tertiary alkyl or an aryl group.

5. A process according to claim 4 wherein R^1 is phenyl or substituted phenyl; R^2 is hydrogen; and R^3 is isopropyl or tert-butyl.

6. A process according to claim 5 wherein a precursor to albuterol is reduced to albuterol.

7. A process according to claim 6 wherein a precursor to albuterol is reduced to predominantly (R)-albuterol in the presence of (R)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-
5 c][1,3,2]oxazaborole.

8. A process for producing (S)-albuterol comprising reacting methyl 5-((1,1-dimethylethyl)imino)acetyl-2-hydroxybenzoate with borane-dimethylsulfide in the presence of (S)-
5 tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-

c][1,3,2]oxazaborole.

9. A process for producing (R)-albuterol comprising reacting methyl 5-((1,1-dimethylethyl)imino)acetyl-2-hydroxybenzoate with borane-dimethylsulfide in a suitable solvent in the presence of (R)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole.

5 10. A process according to claim 9 wherein said solvent is toluene.

11. A process according to claim 9 wherein said reaction is carried out at a temperature between about -20°C and +20°C.

12. A process according to claim 9 wherein said reaction is carried out by adding a solution of methyl 5-((1,1-dimethylethyl)imino)acetyl-2-hydroxybenzoate to a solution of borane-dimethylsulfide and (R)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole.

5 13. A process according to claim 9 wherein said reaction is carried out by adding a solution of methyl 5-((1,1-dimethylethyl)imino)acetyl-2-hydroxybenzoate and a solution of borane-dimethylsulfide simultaneously to a solution of (R)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US95/04869

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07C 209/28, 311/08

US CL :564/99, 356, 357, 361, 363, 365, 415, 489

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 564/99, 356, 357, 361, 363, 365, 415, 489

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J. Med. Chem., Volume 14, issued 17 April 1971, Hartley et al., "Absolute Configuration of the Optical Isomers of Salbutamol", pages 895-896.	1-13

Further documents are listed in the continuation of Box C. See patent family annex.

- * Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document published on or after the international filing date
- "L" document which may throw doubt on priority claim(s) or which is used to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "T" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents; such combination being obvious to a person skilled in the art
- "Z" document member of the same patent family

Date of the actual completion of the international search

07 JULY 1995

Date of mailing of the international search report

03 AUG 1995

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